Journal of the American College of Cardiology Vol. 60, No. 18, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.031

Colchicine for Prevention of Early Atrial Fibrillation Recurrence After Pulmonary Vein Isolation

A Randomized Controlled Study

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Objectives The purpose of the present study was to test the potential of colchicine, an agent with potent anti-inflammatory action, to reduce atrial fibrillation (AF) recurrence after pulmonary vein isolation in patients with paroxysmal AF.

Background Proinflammatory processes induced by AF ablation therapy have been implicated in postablation arrhythmia recurrence.

Methods Patients with paroxysmal AF who received radiofrequency ablation treatment were randomized to a 3-month course of colchicine 0.5 mg twice daily or placebo. C-reactive protein (CRP) and interleukin (IL)-6 levels were measured on day 1 and on day 4 of treatment.

Results In the 3-month follow-up, recurrence of AF was observed in 27 (33.5%) of 80 patients of the placebo group versus 13 (16%) of 81 patients who received colchicine (odds ratio: 0.38, 95% confidence interval: 0.18 to 0.80). Gastrointestinal side-effects were the most common symptom among patients receiving active treatment. Diarrhea was reported in 7 patients in the colchicine group (8.6%) versus 1 in the placebo group (1.3%, $p = 0.03$). Colchicine led to higher reductions in CRP and IL-6 levels: the median difference of CRP and IL-6 levels between days 4 and 1 was −0.46 mg/l (interquartile range: −0.78 to 0.08 mg/l) and −0.10 mg/l (−0.30 to 0.10 pg/ml), respectively, in the placebo group versus −1.18 mg/l (−2.35 to −0.46 mg/l) and −0.50 pg/ml (−1.15 to −0.10 pg/ml) in the colchicine group ($p < 0.01$ for both comparisons).

Conclusions Colchicine is an effective and safe treatment for prevention of early AF recurrences after pulmonary vein isolation in the absence of antiarrhythmic drug treatment. This effect seems to be associated strongly with a significant decrease in inflammatory mediators, including IL-6 and CRP. (J Am Coll Cardiol 2012;60:1790–6)

Atrial fibrillation (AF) is the most common sustained arrhythmia and a significant source of morbidity and mortality (1). Radiofrequency ablation of AF, which initially tried to mimic the surgical interventions of atrial compartmentalization (e.g., the Maze-Cox procedure) (2), evolved after the seminal publication of Haïssaguerre et al. (3) on the triggering role of pulmonary veins, into essentially a technique of electrical isolation of the pulmonary veins, which is the mainstay in current AF ablation therapy (4).

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Proinflammatory processes initiated during ablation therapy have been implicated in early AF recurrence (5), and it has been shown that brief administration of corticosteroids can reduce immediate AF recurrences after catheter ablation of AF (6). However, corticosteroids have several unwanted effects that preclude their mid-term or long-term use in postablation patients, especially in a population with a relatively high prevalence of hypertension and coronary and structural heart disease. Colchicine, however, is an agent with potent anti-inflammatory action, shown in a substudy

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Manuscript received June 8, 2012; revised manuscript received July 4, 2012, accepted July 16, 2012.

of the COPPS (Colchicine for the Prevention of the Post-pericardiotomy Syndrome) trial to reduce postoperative AF incidence, without serious adverse effects (7). Colchicine thus can be regarded as an obvious candidate for prevention of post-ablation AF recurrence.

The purpose of the present study was to examine in a randomized, double-blind, controlled trial the potential of colchicine to reduce AF recurrence in a 3-month period after radiofrequency isolation of the pulmonary veins in patients with paroxysmal AF.

Abbreviations and Acronyms

AF = atrial fibrillation
CRP = C-reactive protein
IL = interleukin
IQR = interquartile range
MRAT = macro–re-entrant atrial tachycardia

Methods

Population. This was a double-blind 2-center study. Patients with paroxysmal AF were included who had at least 2 documented episodes within the previous 12 months (either self-terminating within 7 days or cardioverted, medically or electrically, in fewer than 48 h). At least 1 episode should have been documented under treatment with a class Ic or III antiarrhythmic drug. Exclusion criteria were: age older than 80 years, active inflammatory or infectious disease or malignancy, known autoimmune diseases, corticosteroid or other immunosuppressive or immunomodulatory therapy, moderate or severe hepatic impairment (Child-Pugh class B or C), severe renal failure (estimated glomerular filtration rate <30 ml/min per 1.73 m^2), and inability or unwillingness to adhere to standard treatment or to provide consent. The protocol was approved by the institutional review boards. All patients provided informed consent.

Procedures. After a run-in period of 2 months, during which all antiarrhythmic medication was discontinued and other treatment was stabilized, patients underwent AF ablation. Antral pulmonary vein isolation was performed in all patients, with additional ablation of the left atrial isthmus. An irrigated radiofrequency ablation catheter (Thermocool, Biosense Webster, Diamond Bar, California) was used to perform ablation, with the aid of electroanatomical mapping (Carto XP or Carto 3, Biosense Webster). Pulmonary vein potentials were recorded with a circular mapping catheter (Lasso 2515, Biosense Webster) before, during, and after antral ablation. The endpoint of the ablation procedure was the entrance block into all pulmonary veins, as well as noninducibility of AF with atrial burst pacing from the proximal coronary sinus (at a cycle length of 260 ms for three 5-s intervals, followed by decremental pacing until a cycle length of 200 ms or the minimal cycle length with 1:1 capture). If AF was induced, further ablation lesions were delivered and inducibility testing was repeated. Additional ablation of complex atrial fractionated electrograms or extrapulmonary triggering sites was left at the discretion of the operator. A waiting period of 20 min was allowed to affirm absence of re-conduction. All patients were anticoagulated adequately during the ablation and received oral anticoagulation for 3 months after the procedure (anticoagulation thereafter was decided on according to current guidelines).

Blood samples were obtained from a peripheral vein using standard venipuncture techniques to measure interleukin (IL)-6 and C-reactive protein (CRP). Blood was collected into collection tubes without anticoagulant and was centrifuged 30 min after collection (time allowed for clotting) using a centrifuge with an integrated refrigeration system (at 4°C/1000 *g* for 15 min) and were kept at −80°C in multiple aliquots until analysis (each aliquot was thawed and analyzed once, and no aliquots were refrozen). Blood samples for CRP and IL-6 measurement were obtained immediately after ablation (day 1) and after 3 days of colchicine treatment (day 4) using commercially available kits (R&D Systems, Minneapolis, Minnesota).

Standard transthoracic and transesophageal (to affirm absence of atrial thrombi) echocardiography was performed as part of the preablation preparation checklist in all patients (not more than 3 days before ablation) following standardized in-house protocols. For the purposes of this study, digitally stored echocardiography studies were reviewed in a central laboratory and relevant echocardiographic parameters were recorded in the patient case report form.

Study treatments and adverse event monitoring. Patients were randomized to receive colchicine or placebo for 3 months. Colchicine was administered from day 1 (the day of the ablation procedure) at a dose of 0.5 mg twice daily. No antiarrhythmic drugs (class I or III) were allowed during the 3-month study treatment period (nondihydropyridine calcium channel blockers also were not allowed, and beta-blocking agents were allowed only for the indications of heart failure and coronary artery disease, if already taken before inclusion). Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, myotoxicity, and alopecia. To monitor potential subclinical organ toxicity, complete blood counts and standard biochemical analyses (glucose, urea, creatinine, liver enzymes, creatine kinase, lactate dehydrogenase) were performed at 2, 6, and 12 weeks after the procedure.

Follow-up for AF recurrences. The duration of the follow-up was 3 months, starting from the day of the ablation procedure (no blanking period was applied). The main outcome measure was AF recurrence. Episodes of atrial flutter or other macro–re-entrant atrial tachycardia (MRAT) also were considered as recurrences (for the purpose of simplicity, the term *AF recurrence* is used). The patients were followed up with visits on a 2-week basis in a dedicated arrhythmia outpatient clinic. Any of the following was considered to be AF recurrence: symptomatic AF (AF or MRAT of any duration in symptom-triggered electrocardiograms at any time during the study), AF or MRAT of any duration recorded in electrocardiograms obtained during patient visits at the arrhythmia clinic, and AF or MRAT

of at least 30 s duration in 48-h ambulatory electrocardiogram recordings (Holter) performed twice monthly (each patient had 6 48-h Holter recordings during the 3-month study period). Patients who did not appear for more than 1 visit, for more than 1 Holter recording, or both were excluded from analysis to avoid underdetection of AF recurrence.

Statistical analysis. A sample size of 160 (80 in each randomization group) provided 80% possibility to detect a 50% reduction (1-sided) of early AF recurrence (from 40% to 20%) at an alpha level of 0.05. Analysis was performed on an intention-to-treat basis. All patients who received at least 1 dose of study treatment were included (with the exception of those not adhering to follow-up requirements, as already described). Continuous variables were expressed as mean ± standard error of the mean and were compared using the *t* test, if their distribution did not deviate significantly from the normal distribution (tested with the Kolmogorov-Smirnov test). If significant deviation from the normal distribution was found, continuous variables were expressed as median (interquartile range [IQR]) and were compared using nonparametric tests (the Wilcoxon and Mann–Whitney *U* tests). Categorical variables were expressed as percentages and numbers and were compared using the chi-square test. Kaplan-Meier analysis was performed to assess recurrence-free survival, and the log-rank test was used to make comparisons between groups. Multivariate analysis of the association of univariate predictors to AF recurrence was performed using Cox regression. The association of on-treatment levels of proinflammatory biomarkers with the outcome and their interaction with treatment was a prespecified analysis of the study. SPSS software version 17 was used (SPSS, Inc., Chicago, Illinois), and $p < 0.05$ (2-sided) was considered to indicate statistical significance.

Results

Baseline characteristics and study flow. The patient characteristics are presented in Table 1. The 2 groups were well balanced, with equivalent epidemiological profile and background features, including rates of heart failure, coronary artery disease, and valvular heart disease. Of 210 patients initially screened, 170 were randomized (Fig. 1): 85 in the colchicine group and 85 in the placebo group. Four and 5 patients, respectively, failed to appear for more than 1 visit or Holter recording and were excluded from analysis.

Main outcome measure. Recurrence of AF was observed in 27 (33.5%) of 80 patients in the placebo group, compared

Table 1 Patient Characteristics

Feature	Overall (n = 161)	Colchicine Group (n = 81)	Placebo Group (n = 80)	p Value
Epidemiological background				
Age (yrs)	62.0 ± 6.0	62.0 ± 5.9	62.1 ± 6.0	1.00
Male	115 (71%)	60 (74%)	55 (69%)	0.46
BMI (kg/m^2)	26.0 (24.0–28.5)	26.0 (24.0–28.5)	26.0 (24.0–28.8)	0.86
Smoking	58 (36%)	29 (36%)	29 (36%)	0.95
Hypertension	61 (38%)	31 (38%)	30 (38%)	0.92
Diabetes	41 (26%)	21 (26%)	20 (26%)	0.89
Coronary artery disease	55 (34%)	28 (35%)	27 (34%)	0.91
Heart failure	39 (24%)	21 (26%)	18 (23%)	0.61
Valvular heart disease	17 (11%)	10 (12%)	7 (9%)	0.55
Echocardiographic and laboratory parameters				
LV ejection fraction (%)	55 (45–60)	55 (45–60)	55 (45–60)	0.87
LA diameter (mm)	43.5 ± 3.2	43.5 ± 3.2	43.6 ± 3.1	0.76
CRP day 1 (mg/l)	5.3 (4.4–6.7)	5.5 (4.4–6.9)	5.2 (4.4–6.4)	0.48
CRP day 4 (mg/l)	4.4 (3.3–5.4)	3.6 (3.2–5.0)	4.6 (3.6–5.9)	<0.01
IL-6 day 1 (pg/ml)	3.1 (2.6–3.9)	3.2 (2.6–4.0)	3.1 (2.6–3.7)	0.47
IL-6 day 4 (pg/ml)	2.7 (2.1–3.4)	2.6 (2.0–3.1)	3.0 (2.2–3.5)	<0.01
Procedure-related parameters				
Procedure duration (min)	187.7 ± 39.6	190.8 ± 41.4	184.6 ± 37.8	0.32
Acute PV isolation success*	158 (98%)	79 (98%)	79 (99%)	0.95
Noninducibility of AF after ablation	146 (91%)	72 (89%)	74 (93%)	0.56
CAFE ablation	84 (52%)	41 (51%)	43 (54%)	0.62
Treatment				
Beta-blocker	58 (36%)	32 (38%)	27 (34%)	0.55
ACEi/ARB	87 (54%)	45 (56%)	42 (53%)	0.70
CCB	66 (41%)	33 (41%)	33 (41%)	0.95
Statin	60 (37%)	29 (36%)	31 (39%)	0.75

Values are mean ± SD, n (%), or median (interquartile range). *Defined as entrance block into all pulmonary veins.

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AF = atrial fibrillation; BMI = body mass index; CAFE = complex atrial fractionated electrogram; CCB = calcium channel blocker; CRP = C-reactive protein; IL = interleukin; LA = left atrium; LV = left ventricle; PV = pulmonary vein.

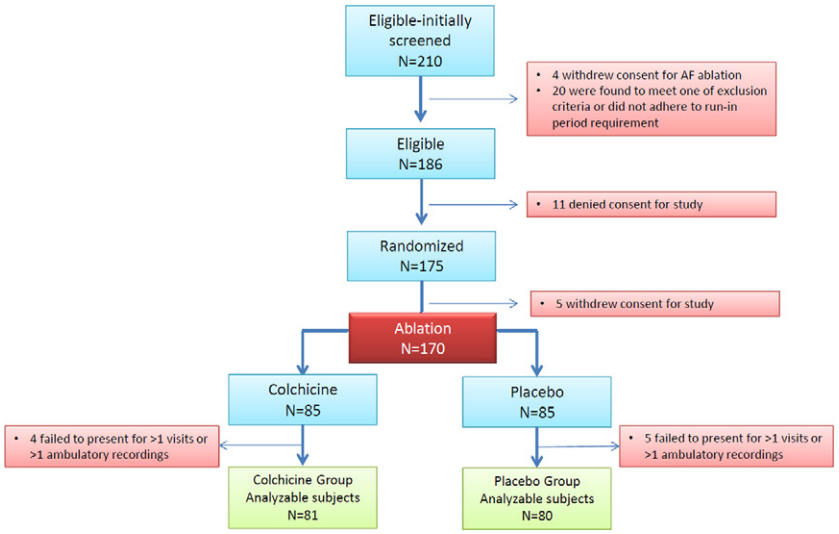

Figure 1 **Study Flow Chart**

Flow diagram of the study.

with 13 (16%) of 81 patients who received colchicine (p = 0.01, odds ratio: 0.38, 95% confidence interval: 0.18 to 0.80). The number needed to treat to prevent 1 case of AF recurrence was 5.6. The Kaplan-Meier analysis showed a significant divergence of the cumulative hazard curves for AF recurrence in the 3 months after the ablation procedure (p = 0.01) (Fig. 2). Mean recurrence-free time was 68.9 days (95% confidence interval: 61.7 to 76.1 days) in the placebo group versus 82.2 days (95% confidence interval: 77.8 to 86.7 days) with colchicine (all subjects without events censored at 90 days). If the 9 patients who were excluded from analysis because of failure to appear for more than 1 visit or Holter recording (Fig. 1) were included (all were free of AF recurrence), the results would not be altered significantly (AF recurrence rate: 31.8% in the placebo group versus 15.3% in the colchicine group, p = 0.01, univariate odds ratio: 0.39).

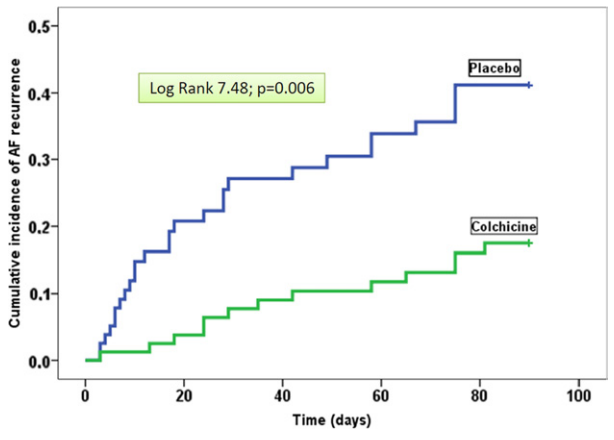

Figure 2 **Atrial Fibrillation Recurrence in the 2 Treatment Groups**

Kaplan-Meier curves of the cumulative hazard of atrial fibrillation (AF) recurrence within 3 months after pulmonary vein isolation according to treatment randomization.

Response of inflammatory markers to treatment. The median levels of CRP and IL-6 on day 1 were similar in the 2 groups, as expected, whereas there was a significant difference on day 4, with higher CRP and IL-6 levels in the placebo group (Table 1). Colchicine led to a significantly higher reduction in CRP and IL-6 levels: the median difference in CRP and IL-6 levels between days 4 and 1 (day 4 levels minus day 1 levels) was −0.46 mg/l (IQR: −0.78 to 0.08 mg/l) and −0.10 pg/ml (IQR: −0.30 to 0.10 pg/ml), respectively, in the placebo group, compared with −1.18 mg/l (IQR: −2.35 to −0.46 mg/l) and −0.50 pg/ml (IQR: −1.15 to −0.10 pg/ml) in the colchicine group (p < 0.01 for both comparisons).

Adverse events and treatment discontinuation. Gastrointestinal side-effects of colchicine (mainly diarrhea and nausea) were the most common ones reported, with higher frequency among patients receiving active treatment compared with those in the placebo group. Diarrhea was reported in 7 (8.6%) of 81 patients of the colchicine group versus 1 (1.3%) of 80 in the placebo group (p = 0.03). Four (4.9%) patients receiving colchicine reported nausea versus 3 patients (3.8%) receiving placebo (p = 0.71). No cases of alopecia or myelotoxicity were recorded. One case of transaminase elevation higher than the upper limit of normal was reported in the colchicine group, which was reversed completely after interruption of treatment (the patient was

Table 2 Univariate Predictors of Atrial Fibrillation Recurrence

	AF Recurrence (n = 40)	No AF Recurrence (n = 121)	p Value
Age (yrs)	63.8 ± 0.9	61.4 ± 0.5	0.03
Randomization to active treatment	13 (33%)	68 (56%)	0.01
Hypertension	26 (65%)	35 (29%)	<0.01
LA diameter (mm)	46 (44–48)	42 (40–45)	<0.01
CRP day 1 (mg/l)	6.8 (5.5–7.3)	5.1 (4.2–6.0)	<0.01
CRP day 4 (mg/l)	5.7 (5.2–6.6)	3.6 (3.2–4.6)	<0.01
IL-6 day 1 (pg/ml)	4.0 (3.2–4.2)	3.0 (2.5–3.5)	<0.01
IL-6 day 4 (pg/ml)	3.5 (3.1–3.9)	2.4 (2.0–3.0)	<0.01

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

asymptomatic, without elevation of bilirubin). No serious adverse events were reported (i.e., fatal or life-threatening events or those requiring hospitalization or medical intervention). Treatment discontinuation before the end of the study was reported in 10 (12.3%) patients in the colchicine group versus 5 (6.3%) patients in the placebo group (p = 0.18). In most of these cases, treatment was administered for a substantial period: discontinuation before completing at least 1 month of treatment was reported in only 3 cases in the colchicine group and 1 in the placebo group.

Predictors of AF recurrence. Patients with recurrence of AF were older than those without recurrence. They had, as expected, a larger left atrium, and the prevalence of hypertension among them was more than double that among patients without recurrence (Table 2). The CRP and IL-6 levels, both immediately after ablation (day 1) and on day 4, were correlated positively with the probability of AF recurrence (Table 2). The AF recurrence rate in the upper quartile of IL-6 day 4 levels was 57.5% versus 0% in the lowest quartile (p < 0.01) (Fig. 3). The correlation of age to AF recurrence was rather weak, whereas IL-6 levels on day 4 were the most powerful univariate predictor of recurrence (Fig. 4).

Randomization to active treatment with colchicine remained a significant predictor of freedom from AF recurrence after controlling for age, sex, presence of hypertension, and left atrial diameter (multivariate p = 0.007). The proportional hazard ratio in the Cox regression analysis was 0.40 (95% confidence interval: 0.21 to 0.78) for AF recurrence in patients in the colchicine group compared with those in the placebo group. Of interest, if IL-6 levels on day 4 (i.e., on-treatment IL-6) were entered, the overall model changed significantly (chi-square change: 36.3, p < 0.01), and the association of colchicine treatment with the outcome was attenuated markedly (the proportional hazard ratio became 0.64, 95% confidence interval: 0.31 to 1.29, p = 0.21). In the final equation, the day 4 IL-6 level was a significant independent predictor of AF recurrence (proportional hazard ratio: 5.1 per unit of IL-6 increase, 95% confidence interval: 2.9 to 8.9). The same results were derived if on-treatment CRP levels were added to the model (the proportional hazard ratio for colchicine treatment changed to 0.68, 95% confidence interval: 0.34 to 1.38, p = 0.28, when day 4 CRP levels were added to the model). On the contrary, addition of day 1 (baseline) levels of either IL-6 or CRP did not affect the independent association of treatment to the outcome. This means that the effect of colchicine treatment on the occurrence of AF is almost totally explained, from a statistical point of view, by the effect of treatment on the measured proinflammatory biomarkers.

Discussion

The principal finding of the present study was that colchicine, administered after catheter ablation of AF, is a safe and effective medication for prevention of early AF recurrence. Colchicine resulted in significant reductions of proinflammatory biomarkers, namely CRP and IL-6, and this reduction was associated to lower AF recurrence. A relatively low dose was used for this study (0.5 mg twice daily), which may account for the excellent tolerability profile shown during the 3-month treatment, although higher doses (1 mg twice daily) were used in the COPPS study (7), without any serious adverse events.

Colchicine is believed to act through inhibition of microtubule assembly in cells of the immune system, particularly neutrophils, leading to inhibition of several cellular functions, including cytokine production by these cells (7). Its method of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules (8). On the whole, colchicine has a potent anti-inflammatory effect, which was shown in patients who had undergone cardiac surgery to be able to prevent postoperative AF (7). The model of postoperative AF resembles that of early AF recurrence after catheter ablation, because in both of these clinical scenarios,

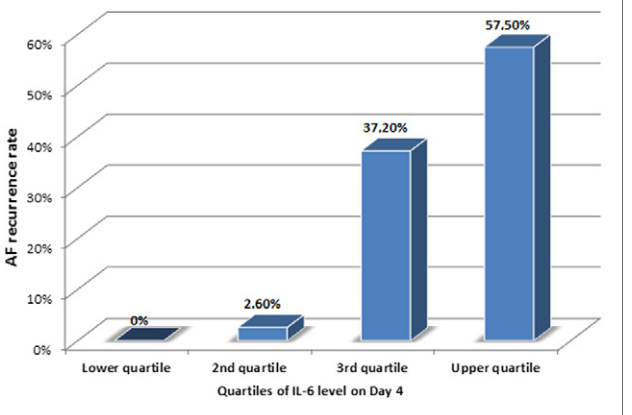

Figure 3 AF Recurrence According to On-Treatment Interleukin 6 Levels

Rate of AF recurrence during the 3-month study period per quartile of on-treatment (day 4) interleukin (IL)-6 levels (p < 0.01 for the differences between quartiles) in the study population (n = 161). Abbreviation as in Figure 2.

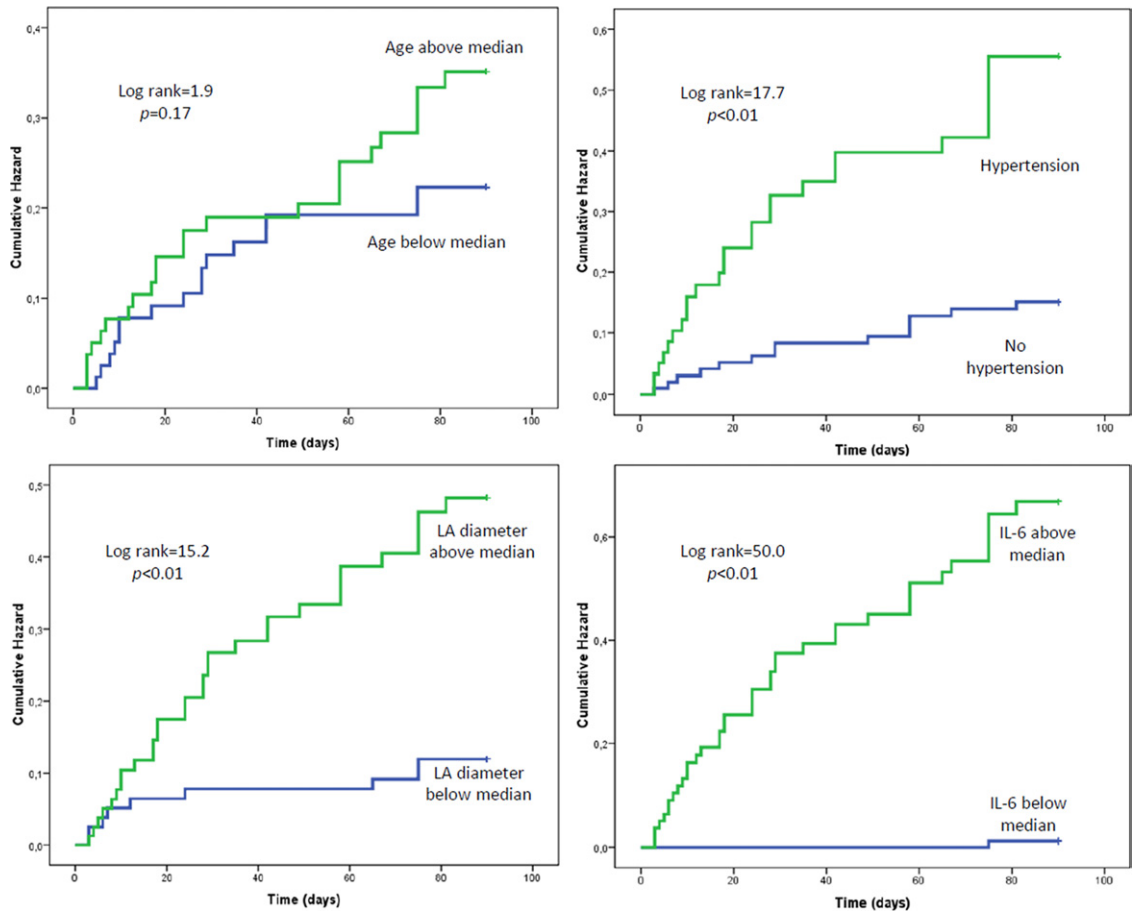

Figure 4 **Predictors of Recurrence**

Kaplan-Meier curves of the cumulative hazard of AF recurrence according to age (dichotomized), presence or absence of hypertension, left atrial (LA) diameter (dichotomized), and on-treatment (day 4) IL-6 levels (dichotomized) in the study population (n = 161). Abbreviations as in Figures 2 and 3.

a strong inflammatory activation comes into play (9,10). After catheter ablation of AF, increased inflammatory biomarkers are correlated to delivered energy and are associated with early recurrence (9). In an early and very interesting study, McCabe et al. (10) showed that CRP levels were increased significantly up to 3 months after AF ablation, as opposed to ablation of supraventricular tachycardia. Further, CRP was associated significantly with AF recurrence before the first follow-up visit (37 to 93 days after ablation). This protracted increase of inflammatory markers after AF ablation constituted the basis for choosing the treatment period for our study (3 months), although intuitively one would think that inflammatory processes after ablation should recede in a more timely manner. The persistent effect of acute factors influencing AF recurrence over the first few weeks after ablation is reflected in recently published guidelines defining the time frame of early AF recurrence at 3 months after ablation (4), which coincides with the blanking period used in several trials of AF catheter ablation (11). Of note, although recurrences during the blanking period are not considered to be treatment failures, their prognostic value for later AF recurrence is high, as repeatedly shown in studies involving relatively large numbers of patients (12,13). In the 5A (Antiarrhythmics After Ablation of Atrial Fibrillation) study, lack of early AF recurrence during the initial 6-week blanking period was the only predictor of 6-month freedom from AF (14). Therefore, prevention of early recurrences seems to be a clinically relevant objective.

Anti-inflammatory treatment as a means of reducing very early recurrences after AF ablation has been reported in the past by Koyama et al. (6), who showed that a short course of corticosteroids indeed was effective in that respect. It is interesting, however, that in the case of corticosteroids, an effect was seen only in the first few days after ablation (designated by the authors as an immediate recurrence), whereas no difference was observed 4 to 30 days after the procedure. The difference from the effect of colchicine on AF recurrence observed in our study may be explained by the different treatment duration. A more prolonged course

of corticosteroid treatment is precluded by their serious potential side-effects, whereas colchicine seems to be suitable for safe midterm administration. Differences of effect also can be attributed to specific features of the method of action of these drugs: in addition to neutrophils and other immune cells, colchicine may affect cardiac myocytes directly, because microtubules play important roles in ion transport modulation, adrenergic stimulation, and intercellular interactions (15–17). Functional parameters and biosynthesis, localization, activity, and degradation of calcium and potassium channels have been linked to the polymerization and depolymerization of microtubules (18), whereas proliferation of microtubules in experimental models of stretch-induced arrhythmia increased the arrhythmogenic effect of transient diastolic stretch (19). As a result, colchicine may exert direct effects on the atrial electrical substrate, in addition to its anti-inflammatory action.

Study limitations. In studies of AF recurrence, there is always an issue of adequate detection of recurrences, considering that a large proportion of AF episodes are asymptomatic (4). The negative predictive value of prolonged Holter recordings is moderate at best (20). However, in the present study, an intensive follow-up protocol was observed with a great number of visits and Holter recordings per patient, aiming at maximizing the efficiency of AF detection. More importantly, it was the difference in the incidence of AF recurrence between the 2 groups—not the absolute recurrence rate—that mattered in this study. Consequently, because there is no reason to believe that AF detection preferentially was more or less efficient in 1 of the 2 treatment arms, the issue of adequate AF detection should not have influenced in any way the main conclusions of this study. Another aspect of the present study that would need clarification, if colchicine was to be used in this context, is the required length of treatment after AF ablation. We selected a 3-month treatment period based on past reports on proinflammatory activation after ablation (10), but it is nevertheless conceivable that a different duration of treatment also could be effective.

Conclusions

Colchicine is an effective and safe treatment for prevention of early AF recurrences after radiofrequency pulmonary vein isolation, in the absence of antiarrhythmic drug treatment. This effect seems to be associated strongly with a significant decrease in inflammatory mediators, including IL-6 and CRP. These results, should they be confirmed, suggest a role for colchicine in the therapeutic management of patients undergoing catheter ablation of AF.

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Key Words: ablation ■ atrial fibrillation ■ colchicine ■ C-reactive protein ■ inflammation ■ interleukin-6 ■ radiofrequency.